Engsig, F. N., Zangerle, R., Katsarou, O., Dabis, F., Reiss, P., Gill, M. J., ... The Antiretroviral Therapy Cohort Collaboration (ART-CC) and the Collaboration of Observational HIV Research Europe (COHERE) in EuroCoord (2014). Long-term mortality in HIV positive individuals virally suppressed for more than three years with incomplete CD4 recovery. Clinical Infectious Diseases, 58, 1312-1321. 10.1093/cid/ciu038

Title

Long-term mortality in HIV positive individuals virally suppressed for more than three years with incomplete CD4 recovery.

Authors

Frederik N Engsig[1,2], Robert Zangerle[3], Olga Katsarou[4], Francois Dabis[5], Peter Reiss[6], John Gill[7], Kholoud Porter[8], Caroline Sabin[9], Andrew Riordan[10], Gerd Fätkenheuer[11], Félix Gutiérrez[12], Francois Raffi[13], Ole Kirk[1,14], Murielle Mary-Krause[15], Christoph Stephan[16] , Patricia Garcia de Olalla[17], Jodie Guest[18], Hasina Samji[19], Antonella Castagna[20], Antonella d'Arminio Monforte[21], Adriane Skaletz-Rorowski[22], Jose Ramos[23], Giuseppe Lapadula[24], Cristina Mussini[25], Lluís Force[26], Laurence Meyer[27], Fiona Lampe[28], Faroudy Boufassa[29], Heiner C Bucher[30], Stéphane De Wit[31], Greer A Burkholder[32], Ramon Teira[33], Amy C Justice[34,35], Tim R Sterling[36], Heidi Crane[37], Jan Gerstoft[1], Jesper Grarup[14], Margaret May[38], Geneviève Chêne[5], Suzanne M Ingle[38], Jonathan Sterne[38] and Niels Obel[1]. The Antiretroviral Therapy Cohort Collaboration (ART-CC) and the Collaboration of Observational HIV Research Europe (COHERE) in EuroCoord.

Affiliations

[1]Department of Infectious Diseases, Rigshospitalet, Copenhagen University Hospital, Denmark.

[2] Department of Microbiological Diagnostics & Virology, Statens Serum Institut, Denmark

[3] Department of Dermatology and Venerology, Innsbruck Medical University, Innsbruck, Austria.

[4] Blood Centre and National Reference Centre for Congenital Bleeding Disorders, Laiko General Hospital, Athens, Greece.

[5] University Bordeaux, ISPED, Centre Inserm U897- Epidemiologie-Biostatistique, Bordeaux, France.

[6] Academic Medical Center, Department of Global Health, Amsterdam Institute for Global Health and Development, and Division of Infectious Diseases, University of Amsterdam, and Stichting HIV Monitoring, Netherlands.

[7] Department of Medicine, University of Calgary, Calgary, Alberta Canada .

[8] MRC Clinical Trials Unit at University College London (UCL), London, UK.

[9] Research Department of Infection and Population Health, UCL, London, United Kingdom.

[10] Department of Paediatric Infectious Diseases and Immunology, Alder Hey Children´s NHS Foundation Trust, Liverpool, United Kingdom.

[11] First department of Internal Medicine, University of Cologne, Germany.

[12] Infectious Diseases Unit, Hospital General Universitario de Elche, Universidad Miguel Hernández, Alicante, Spain

[13] Infectious Diseases Department and HIV Clinical Research Unit, Hotel Dieu University Hospital, Nantes, France.

[14] Copenhagen HIV Programme, Panum Institute, University of Copenhagen, Denmark

[15] L'Institut National de la Santé et de la Recherche Médicale (INSERM), Unité Mixte de Recherche en Santé 943, University Pierre and Marie Curie, Hospital Pitie-Salpetriere, Paris, France.

[16] Department of Infectious Disease, Goethe University Hospital, Frankfurt/Main, Germany

[17] Epidemiology Service, Public Health Agency of Barcelona, Spain.

[18] Atlanta Veterans Affairs Medical Center, Atlanta, Georgia, United States of America.

[19] British Columbia Centre for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada.

[20] Department of Infectious and Tropical Diseases, San Raffaele Scientific Institute, Milan, Italy.

[21] Infectious Diseases Unit, Department of Health Sciences, San Paolo University Hospital, Milan, Italy.

[22] Competence Network for HIV/AIDS, Ruhr-Universität Bochum, Bochum, Germany.

[23] Pediatrics Department, Hospital Universitario de Getafe, Madrid, Spain.

[24] Division of Infectious Diseases, Department of Internal Medicine, "San Gerardo" Hospital, University of Milan-Bicocca, Monza, Italy.

[25] Clinic of Infectious Diseases Department of Internal Medicine and Medical Specialties University of Modena and Reggio Emilia Modena, Italy.

[26] Infectious Diseases Unit, Hospital de Mataró, Mataró, Barcelona, Spain.

[27] Service d'Epidémiologie et de Santé Publique, Hôpital de Bicêtre, AP-HP; INSERM U1018; Université Paris-Sud, France.

[28] Research Department of Infection and Population Health, University College London, United Kingdom.

[29] Inserm, CESP Centre for Research in Epidemiology and Population Health, Epidemiology of HIV and STI Team, Université Paris-Sud, Le Kremlin Bicêtre, France.

[30] Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Basel, Switzerland.

[31] Department of Infectious Diseases, St Pierre University Hospital, Brussels, Belgium.

[32] Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham, Alabama, United States of America.

[33] Servicio de Medicina Interna, Hospital de Sierrallana Torrelavega, Cantabria, Spain.

[34] VA Conneticut Healthcare System, West Haven, Conneticut, United States of America.

[35] Department of Internal Medicine, Yale University School of Medicine, New Haven, Conneticut, United States of America.

[36] Division of Infectious Diseases, Vanderbilt University School of Medicine, Nashville, Tennessee, United States of America

[37] Clinical Epidemiology and Health Services Research Core, Center for AIDS Research, University of Washington, United States of America.

[38] School of Social and Community Medicine, University of Bristol, Bristol, UK.

Corresponding author

Dr. Frederik Neess Engsig, Dept. of Infectious Diseases, Rigshospitalet, Copenhagen University. Blegdamsvej 9, DK2100 Copenhagen Ø, Denmark, Tel: 004635457726. Fax: 004535456648.

Email: fren74@gmail.com

Running head

Virally suppressed HIV positive individuals on cART who do not achieve CD4 count >200 cells/μL have substantially increased long-term mortality. The increased mortality was seen across different patient groups and for all causes of death.

Keywords

HIV, CD4 cell recovery, sustained viral suppression, risk factors, mortality

Abstract:

Background

Some HIV infected individuals initiating combination antiretroviral therapy (cART) with low CD4 counts achieve viral suppression but not CD4 cell recovery. We aimed to identify (1) risk factors for failure to achieve CD4 count >200 cells/μL after three years of sustained viral suppression and (2) the association of achieved CD4 count with subsequent mortality.

Methods

We included treated HIV infected adults from two large international HIV cohorts, who were virally suppressed (≤500 HIV-1 RNA copies/ml) for >3 years with CD4 count ≤200 cells/μL at start of the suppressed period. Logistic regression was used to identify risk factors for incomplete CD4 recovery (≤200 cells/μL) and Cox regression to identify associations with mortality.

Results

Of 5550 eligible individuals, 835 (15%) did not reach CD4 count >200 cells/μL after three years of suppression. Increasing age, lower initial CD4 count, male heterosexual and injection drug use transmission, cART initiation after 1998 and longer time from initiation of cART to start of the virally suppressed period were risk factors for not achieving CD4 count >200 cells/μL. Individuals with CD4 ≤200 cells/μL after three years of viral suppression had substantially increased mortality (adjusted hazard ratio 2.60; 95% confidence interval 1.86-3.61) compared to those who achieved CD4 count >200 cells/μL. The increased mortality was seen across different patient groups and for all causes of death.

Conclusions

Virally suppressed HIV positive individuals on cART who do not achieve CD4 count >200 cells/μL have substantially increased long-term mortality.

Main manuscript:

Introduction

The introduction of combination antiretroviral therapy (cART) has decreased morbidity and mortality in HIV positive individuals due to viral suppression and CD4 cell recovery (1-3). However, some individuals treated with cART achieve viral suppression but not CD4 cell recovery (4-6). Several studies have shown that individuals with successful virological response to cART and incomplete CD4 recovery have increased mortality (4;5;7-9). However, the only previous study exclusively examining the long-term mortality in individuals started late on cART with sustained viral load (VL) suppression and low CD4 count is limited by small sample size (8).

By combining data from two large international collaborations of HIV cohorts, The Antiretroviral Therapy Cohort Collaboration (ART-CC) and The Collaboration of Observational HIV Epidemiological Research Europe (COHERE), we examined risk factors for failure to achieve CD4 recovery among treated individuals who were virally suppressed for more than three years, and compared mortality rates after three years of viral suppression according to CD4 count reached at end of the virally suppressed period.

Methods

Setting and participants

The ART-CC is an international collaboration of 18 cohort studies of HIV-1 positive individuals from Europe and North America which was established in 2000 to examine the prognosis of HIV-1 positive, treatment-naive individuals initiating cART (10). COHERE was established in 2005 and is an international collaboration of 35 cohorts from 29 European countries. The COHERE data were pooled within the EuroCoord network (www.EuroCoord.net). Each collaboration focuses on scientific questions requiring large sample sizes, which the contributing cohorts cannot answer individually (11). Further information about the two collaborations is available at http://www.art-cohort-collaboration.org and http://www.COHERE.org.

Study population and design

We identified all HIV-1 positive individuals who: 1) were >16 years old at start of the suppressed period, 2) were on cART continuously (defined in ART-CC as treatment with at least 3 drugs from 2 different classes and in COHERE as the concomitant use of at least three antiretroviral drugs) for at least three years, 3) after start of cART had a period with suppressed VL of at least three years (all VL≤500 HIV-1 RNA copies/ml and never a time span of more than 7 months between VL measurements), 4) had a CD4 cell count ≤200 cells/μL at the start of the virally suppressed period (figure 1). Individuals enrolled in more than one cohort were identified and only one record per individual was included. A VL cut-off of ≤500 copies/ml was chosen in order to overcome the heterogeneity of the assay detection limits used during the study period.

Statistical Analysis

Risk factors for failure to achieve a CD4 count >200 cells/μL after three years of viral suppression

We used logistic regression to identify risk factors for not achieving CD4 count >200 cells/μL after three years of sustained viral suppression. We assessed the effect of CD4 count at the start of the suppressed period as a categorical variable (0-25, 26-50, 51-100, 101-150 and 151-200 cells/μL). In a sensitivity analysis, we fitted separate models for each of these CD4 strata. The following variables were included in all models: age at start of virally suppressed period (years; <30, 30-39, 40-49, ≥50), probable route of infection/gender (men who have sex with men (MSM), male heterosexuals, female heterosexuals, injection drug use (IDU), other/unknown (the number of male and female IDUs and other/unknowns did not allow for further classification according to gender), pre-cART VL (last VL available within three months before start of cART or first VL within a month after start of cART if the former was not available; VL <100,000 copies/ml, ≥100,000 copies/ml and missing), year of cART initiation (1996-1997, 1998-2000, 2001-), time from cART initiation to start of suppressed period (<12 months, ≥12 months), AIDS (no AIDS event, ≥1 AIDS event before start of the virally suppressed period). We tested for interactions between pairs of variables.

Risk factors for mortality after 3 years of viral suppression

Person-years at risk were calculated from the date of the first CD4 count within three months after three years of viral suppression to the earlier of time of death, loss to follow-up or end of observation. We estimated mortality rates and Kaplan Meier plots according to CD4 count at the end of the three year virally suppressed period (≤200, 201-350, 351-500 or >500 cells/μL) and used Cox regression to estimate hazard ratios (HR) for death according to these CD4 count groups. All analyses were adjusted for the covariates listed above (AIDS events in this analysis were up to the

end of the virally suppressed period) and stratified by cohort. We used Cox regression to compare individuals with CD4 counts ≤200 cells/μL and >200 cells/μL at the end of the suppressed period within strata defined by: age at start of virally suppressed period, route of infection/gender, AIDS status, and CD4 at start of suppressed period. In sensitivity analyses we (1) used a cut-off value of 50 copies/ml to define viral suppression and (2) included only study subjects reporting sexual route of transmission and no positive test for hepatitis C virus (HCV) co-infection (HCV was defined as a positive test for HCV RNA or a positive test for HCV IgG antibody at any time during follow-up).

Analysis of causes of death

COHERE does not collect data on causes of death, so these analyses were restricted to individuals included in ART-CC. Online supplement 1 describes how the causes of death data in this study were assigned and categorized. Causes of death were further categorized as AIDS defining, non-AIDS defining, unnatural (accident/violent/suicide/drug abuse) and unknown (12). Non-AIDS causes of death were further divided into hepatitis, cancers and other. As analyses of different causes of death can pose the problem of competing risks, we estimated both sub-distribution HRs (using the Fine and Gray approach) and standard (Cox) HRs (adjusted only for age and gender due to the small number of events) (13). Because these estimates did not differ appreciably, we report only the estimates from Cox models. SPSS statistical software, Version 15.0 (Norusis; SPSS Inc., Chicago, Illinois, USA) and R software, version 2.8.1, were used for data analysis.

Results

We identified 113,845 unique HIV-1 positive individuals from the COHERE and ART-CC cohorts, of whom 41,081 were treated with cART for <3 years, 50,495 did not have sustained viral suppression and 368 had no available CD4 measurement at the start of the suppressed period. Of

21,901 individuals who achieved sustained viral suppression for three years or more, 16,193 had CD4 count >200 cells/μL at start of the virally suppressed period and 158 had no available CD4 measurement at the end of the suppressed period, leaving 5550 individuals (20,291 person years of observation, median follow-up time 3.4 years, IQR 1.6–5.3 years) eligible for analyses (figure 1). A histogram of the distribution of CD4 count at the start of the virally suppressed period is shown in online supplement 2. The majority of these (4715; 85.0%) achieved CD4 count >200 cells/μL after three years of viral suppression. Half (2904; 52.3%) were aged >40 years at the start of the suppressed period (table 1).

Risk factors for failure to achieve CD4 count >200 cells/μL

We found that risk of failure to achieve a CD4 count >200 cells/μL increased with increasing age and with decreasing CD4 count at start of the virally suppressed period (table 2). Compared with MSM, males with heterosexual route of infection, IDU, and those with other or unknown transmission group had greater risk of incomplete CD4 recovery. Risk was also greater in those whose last viral load before start of cART was <100,000 copies/ml, those who initiated cART after 1998 and those who had 12 months or more from initiation of cART to start of the virally suppressed period. In models stratified on CD4 at start of the suppressed period, the impact of age and AIDS defining illness on incomplete CD4 recovery appeared similar across CD4 strata (online supplement table 1). Patients infected via IDU had consistently higher risk of incomplete CD4 recovery than those infected via MSM.

Time to death from any cause

A total of 175 (3.2%) individuals died: 66 (7.9%) of those who did not attain CD4 count >200 cells/μL and 109 (2.3%) of those who attained CD4 count >200 cells/μL. Table 3 shows that individuals who did not attain CD4 count >200 cells/μL after three years of sustained viral suppression had substantially increased mortality compared with those who achieved CD4 count

>200 cells/μL (adjusted HR (95% CI); 2.60 (1.86-3.81)). The cumulative probability of survival stratified by CD4 count are presented in figure 2. The estimated 5-year cumulative mortality (95%CI) was 11.8% (8.9%-15.2%) in patients with CD4 count <200 cells/μL at the end of the suppressed period, compared with 4.1% (3.1%-5.3%), 2.2% (1.4%-3.4%) and 2.2% (1.2%-3.7%) in patients with CD4 count 201-350, 351-500 and >500 cells/μL at the end of the suppressed period. Compared to individuals with CD4 count >500 cells/μL at the end of the suppressed period, adjusted HR (95%CI) in individuals with 351-500, 201-350 and ≤200 CD4 cells/μL were 0.62 (0.32-1.19), 1.28 (0.74-2.23) and 2.62 (1.47-4.67), respectively.

Mortality hazard ratios stratified on risk factors

Table 3 shows that the impact on mortality of not achieving CD4 count >200 cells/μL was most pronounced in individuals whose CD4 count at the start of the suppressed period was 151-200 cells/μL (those in whom the increase in CD4 since start of ART was lowest). However, estimated hazard ratios within CD4 strata were estimated imprecisely, and their confidence intervals overlapped. The impact of incomplete CD4 recovery appeared similar across strata defined by age, mode of transmission, viral load before start of cART, year of cART initiation, time from initiation of cART to start of the virally suppressed period and AIDS defining disease (table 3).

Sensitivity analyses

Of 2692 individuals who were eligible when a cut-off of 50 copies/ml for viral suppression was used, 2253 (83.7%) achieved CD4 count >200 cells/μL. Estimated effects of risk factors for not achieving a CD4 count >200 cells/μL were broadly similar to those in the main analyses, although there was less evidence of elevated risk among heterosexual males (adjusted odds ratio (95%CI); 1.17 (0.88-1.55)) and females (0.64 (0.45-0.93)) (online supplement table 2). In this analysis a total of 33 (7.5%) and 41 (1.8%) individuals with and without incomplete CD4 recovery respectively died during follow-up, and the adjusted HR for not attaining (compared with attaining) CD4 count

>200 cells/μL was 3.96 (95% CI; 2.36 – 6.66). Exclusion of 1625 (29.3%) individuals who did not report sexual route of transmission nor had HCV co-infection left 3925 individuals with 87 deaths. The adjusted HR for not attaining (compared with attaining) CD4 count >200 cells/μL was 2.98 (95% CI; 1.85 – 4.79).

Time to death from specific causes

Of 4135 individuals included in analyses of cause-specific mortality, 619 (15.0%) did not attain CD4 count >200 cells/μL after the suppressed period and 121 (2.9%) died. Most deaths were from non-AIDS defining causes, in both groups (table 4). Mortality due to AIDS-defining, non-AIDS defining and unnatural causes of death was increased substantially in individuals who did not attain CD4 count >200 cells/μL and was highest for hepatitis and non-AIDS defining cancers (adjusted HRs (95%CI); 6.76 (1.93–23.74) and 2.89 (1.44-5.28)).

Discussion

Based on data combined from two large international HIV cohort collaborations, we found that among HIV positive individuals with three years of viral suppression on cART, those with incomplete CD4 recovery (CD4 count ≤200 cells/μL) had markedly higher mortality rates than those who achieved CD4 count >200 cells/μL. These higher rates were observed consistently across strata defined by age, gender, transmission group and prior AIDS-defining illness. Rates of both AIDS- and non-AIDS-defining causes of death were elevated. We identified older age, transmission via male heterosexual sex or IDU, lower CD4 count at start of the suppressed period and longer time from initiation of cART to start of the virally suppressed period as risk factors for incomplete CD4 cell recovery.

Strengths and weaknesses.

Since 15% of treated HIV positive individuals have CD4 count <200 cells/μl after long-term viral suppression, prognosis of such patients is a major concern. By combining data from two collaborations of HIV cohort studies, we assembled a sufficiently large dataset to permit us to examine both risk factors and prognosis for all-cause and cause-specific mortality among patients with incomplete CD4 recovery. The contributing cohort studies represent a wide variety of countries and settings, and our results are therefore likely to be generalizable to treated HIV positive people in Western Europe and North America. Not all contributing cohorts link their data with national death registries, which may lead to an underestimation of mortality rates. However estimates of relative mortality comparing different groups should not be biased, providing that non-ascertained deaths are missing at random (MAR) (14). Serological tests for co-infection with HCV were not performed systematically in all cohorts, therefore some co-infected individuals may have been misclassified. However, findings were similar in a sensitivity analysis excluding both IDUs and HCV co-infected individuals, and the impact of misclassification of HCV sero-status may have

been limited because of its strong association with transmission via IDU, which was available from all cohorts. We did not have access to data on smoking, other comorbidity (for example diagnosis of non-AIDS cancers) or non-cART medications (for example cancer chemotherapy) and were therefore not able to adjust for such factors or assess whether they predict incomplete CD4 recovery.

Our definition of CD4 recovery (CD4 count >200 cells/μL after three years of viral suppression following cART initiation) differs from other definitions of recovery: for example NIH guidelines defined an adequate response as an increase in CD4 count in the range of 50 to 150 cells/μL per year (15). Our definition of CD4 recovery was based on two considerations. First, the increase in CD4 count over time since start of cART in virologically suppressed patients depends on baseline CD4 count (6). Second, the risk of mortality is strongly related to current CD4 count (16;17).

Results in context with other literature

Previous studies have identified age (8;18;19) and low baseline CD4 counts (4;18;20) as risk factors for incomplete CD4 cell recovery. However two of these (16;20) used designs that differed from ours in terms of inclusion criteria and length of the virally suppressed period. The effect of age observed in our study is consistent with its association with thymus size and activity and suggests that initiation of cART before immune-incompetence is especially important in older HIV individuals (21-23).

Most studies that examined clinical endpoints according to achieved CD4 count in virally suppressed patients used short periods of viral suppression or did not have inclusion criteria relating to baseline CD4 count (9;17;24). These studies mainly estimated short term effects of changes in CD4 count, rather than elucidating the long term impact of sustained low CD4 cell counts in long-term virally suppressed patients. Two previous studies examined implications of incomplete CD4

recovery among patients with sustained viral suppression and our findings are in accordance with their estimates. Loutfy et al. observed a 2.69-fold (95% CI 1.26-5.78) increase in mortality comparing 176 patients with CD4 count <200 cells/µl with 1545 patients with CD4 count >200 cells/µl after 2 years of viral suppression (24). That study had both shorter duration of and less strict criteria for viral suppression as well as a much smaller and less generalizable sample. We previously reported the relative risk of death to be 3.4 (95% CI 1.4-8.0) in a small study comparing 55 immunological non-responders with 236 responders in the Danish HIV Cohort Study, using a design almost identical to the present study (8). Data on causes of death were not available in either of these two studies. Although we observed increased mortality in all subgroups of individuals with poor CD4 recovery, the relative risk of death was greatest among individuals with baseline CD4 count between 151 and 200 cells/µL. These individuals are characterized by the lowest increase (or even a decrease) in CD4 counts during the three year period of virological suppression, a phenomenon which may be related to non-HIV comorbidity such as cancer.

Consistent with our results, previous studies have found incomplete CD4 recovery to be associated with an increased risk of non-AIDS cancer (25-27). It is still a matter of debate whether low CD4 counts lead to non-AIDS defining cancers or whether common risk factors lead to low CD4 count and non-AIDS defining cancers. Higher rates of non-AIDS mortality among individuals with incomplete CD4 recovery may be related to chronic immune activation in virally suppressed individuals (28;29).

Implications and conclusions

Our data underline the importance of early diagnosis of HIV and treatment with cART before patients have a low CD4 count. Although we have identified risk factors for poor CD4 recovery, no interventions to increase CD4 count in virally suppressed patients have been demonstrated to have beneficial effects on clinical endpoints and mortality. Previous studies have not consistently

demonstrated differences between antiretroviral drug classes in effects on CD4 increases, and attempts to increase CD4 count with Il-2 were futile in terms of clinical benefit (30-32). Virally suppressed patients with low CD4 counts should be monitored closely for diseases not conventionally considered HIV-related, especially non-AIDS defining cancers and liver diseases. Our study demonstrated an increased risk of non-AIDS causes of death in immunological non-responders: further research is needed to elucidate the mechanisms that lead to persistently low CD4 counts despite viral suppression.

Analysis and writing committee

Frederik N Engsig (Danish HIV Cohort), Robert Zangerle (AHIVCOS), Olga Katsarou (AMACS), Francois Dabis (AQUITAINE), Peter Reiss (ATHENA), John Gill (Alberta HIV clinic), Kholoud Porter (CASCADE), Caroline Sabin (CHIC), Andrew Riordan (CHIPS), Gerd Fätkenheuer (Cologne Bonn), Félix Gutiérrez (CoRIS), Francois Raffi (COPILOTE), Ole Kirk (EuroSIDA), Murielle Mary-Krause (FHDH-ANRS CO4), Christoph Stephan (Frankfurt Cohort), Patricia Garcia de Olalla (GEMES), Jodie Guest (HAVACS), Hasina Samji (HOMER), Antonella Castagna (HSR), Antonella d'Arminio Monforte (ICONA), Adriane Skaletz-Rorowski (KompNet), Jose Ramos (Madrid HIV Cohort), Giuseppe Lapadula (MASTER Cohort), Cristina Mussini (MODENA), Lluís Force (PISCIS), Laurence Meyer (PRIMO), Fiona Lampe (Royal Free), Faroudy Boufassa (SEROCO), Heiner C Bucher (SHCS), Stéphane De Wit (St. Pierre Cohort), Greer Burkholder (UAB), Ramon Teira (VACH), Amy Justice (VACS), Tim R Sterling (Vanderbilt), Heidi Crane (UW), Jan Gerstoft (Danish HIV Cohort), Jesper Grarup (COHERE), Margaret May (ART-CC), Geneviève Chêne (COHERE), Suzanne M Ingle (ART-CC), Jonathan Sterne (ART-CC) and Niels Obel (Danish HIV Cohort)

The ART-CC Steering Committee

Andrew Boulle (IeDEA Southern Africa), Hans-Reinhard Brodt (Frankfurt), Jordi Casabona (PISCIS), Matthias Cavassini (SHCS), Geneviève Chêne (Aquitaine), Dominique Costagliola (FHDH), François Dabis (Aquitaine), Antonella D'Arminio Monforte (ICONA), Julia del Amo (CoRIS-MD), Ard Van Sighem (ATHENA), Gerd Fätkenheuer (Koln/Bonn), John Gill (Alberta HIV clinic), Jodie Guest (HAVACS), David Hans-Ulrich Haerry (EATG), Robert Hogg (HOMER), Amy Justice (VACS), Amanda Mocroft (EuroSIDA), Niels Obel (Danish HIV Cohort), Mari Kitahata (Washington), Fiona Lampe (Royal Free), Peter Reiss (ATHENA), Michael Saag

(Alabama), Tim R Sterling (Vanderbilt-Meherry), Ramon Teira (VACH), Matthew Williams (UK-CAB), Robert Zangerle (AHIVCOS)

ART-CC Coordinating Centre, Bristol University: Suzanne Ingle, Margaret May, Jonathan Sterne

COHERE Steering Committee

Contributing cohorts: Robert Zangerle (AHIVCOS), Giota Touloumi (AMACS), Josiane Warszawski (ANRS CO1 EPF/ANRS CO11 OBSERVATOIRE EPF), Laurence Meyer (ANRS CO2 SEROCO), François Dabis (ANRS CO3 AQUITAINE), Murielle Mary Krause (ANRS CO4 FHDH), Jade Ghosn (ANRS CO6 PRIMO), Catherine Leport (ANRS CO8 COPILOTE), Peter Reiss (ATHENA), Ferdinand Wit (ATHENA), Maria Prins (CASCADE), Heiner C Bucher (CASCADE), Caroline Sabin (CHIC), Diana Gibb (CHIPS), Gerd Fätkenheuer (Cologne Bonn), Julia Del Amo (CoRIS), Niels Obel (Danish HIV Cohort), Claire Thorne (ECS), Amanda Mocroft (EuroSIDA), Ole Kirk (EuroSIDA), Christoph Stephan (Frankfurt), Santiago Pérez-Hoyos (GEMES-Haemo), Osamah Hamouda (German ClinSurv), Barbara Gussenheimer-Bartmeyer (German ClinSurv), Antoni Noguera-Julian (NENEXP and CORISPE-cat), Andrea Antinori (ICC), Antonella d'Arminio Monforte (ICONA), Norbert Brockmeyer (KOMPNET), José Ramos (Madrid Cohort), Manuel Battegay (MoCHIV and SHCS), Andri Rauch (SHCS), Cristina Mussini (Modena Cohort), Pat Tookey (NSHPC), Jordi Casabona (PISCIS), Jose M. Miró (PISCIS), Antonella Castagna (San Raffaele), Stephane de Wit (St. Pierre Cohort), Tessa Goetghebuer (St. Pierre Paediatric Cohort), Carlo Torti (Italian Master Cohort), Ramon Teira (VACH), Myriam Garrido (VACH). Paediatric cohort representatives: Ali Judd, Josiane Warszawski. European AIDS Treatment Group: David Haerry.

COHERE Executive Committee

Ian Weller (Chair, COHERE), Jordi Casabona (PISCIS), Dominique Costagliola (FHDH), Antonella d'Arminio-Monforte (ICONA), Manuel Battegay (MoCHIV and SHCS), Stephane de Wit (St. Pierre Cohort), Julia Del Amo (CoRIS), Jesper Grarup (Head, Copenhagen Regional Coordinating Centre), Geneviève Chêne (Head, Bordeaux Regional Coordinating Centre).

COHERE Regional Coordinating Centres (RCC)

Bordeaux RCC: Céline Colin, Christine Schwimmer, Monique Termote, Diana Barger; Copenhagen RCC: Jesper Kjaer, Maria Campbell, Dorthe Raben.

Project leaders and statistical analysis

Manuel Battegay, Julia Bohlius, Vincent Bouteloup, Heiner Bucher, Alessandro Cozzi-Lepri, François Dabis, Antonella d'Arminio Monforte, Julia del Amo, Maria Dorrucci, Matthias Egger, Frederik Engsig, Hansjakob Furrer, Ali Judd, Ole Kirk, Olivier Lambotte, Charlotte Lewden, Sara Lodi, Rebbeca Lodwick, Sophie Matheron, Laurence Meyer, Jose Miro, Amanda Mocroft, Susana Monge, Fumiyo Nakagawa, Niels Obel, Roger Paredes, Andrew Phillips, Massimo Puoti, Joanne Reekie, Caroline Sabin, Alexandra Scherrer, Colette Smit, Jonathan Sterne, Rodolphe Thiebaut, Claire Thorne, Carlo Torti, Giota Touloumi, Linda Wittkop.

Funding

The COHERE study group has received generic funding from: Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS), France; HIV Monitoring Foundation, the Netherlands; and the Augustinus Foundation, Denmark. The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under EuroCoord grant agreement n° 260694. The EuroCoord acknowledgment appendix may be found at

http://www.cphiv.dk/COHERE/StudyDocuments/tabid/298/Default.aspx. A list of the funders of the participating cohorts can be found on the COHERE website at http://www.cohere.org.

The ART Cohort Collaboration was funded by UK Medical Research Council (MRC) grants G0700820 and MR/J002380/1

The funders had no role in the study design; in the collection, management, analysis, and interpretation of data; in the preparation, review, or approval of the manuscript, or in the decision to submit the article for publication. The researchers are independent from the funders.

Conflicts of interest

Potential competing interests: Niels Obel has received research funding from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, GlaxoSmithKline, Abbott, Boehringer Ingelheim, Janssen-Cilag and Swedish Orphan. Frederik N Engsig has received research funding from Merck Sharp & Dohme. Jan Gerstoft has received research funding from Abbott, Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Pharmasia, GlaxoSmithKline, Swedish Orphan and Boehringer Ingelheim. Heiner C. Bucher has received travel grants, honoraria and unrestricted research grants from various pharmaceutical companies including, GlaxoSmithKline, Bristol-Myers-Squibb, Gilead, Janssen, Roche, Abbott, Tibotec, Boehringer-Ingelheim and ViiV Healtcare. Heiner C. Bucher is supported by grants from Santésuisse and the Gottfried and Julia-Bangerter-Rhyner-Foundation. Felix Gutiérrez has received research funding from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmith-Kline, Janssen-Cilag, Merck Sharp & Dohme, Pfizer, and ViiV Healthcare. In the past 3 years, Geneviève Chêne has received consulting fees (Scientific Committee) from the French Agency for Research on AIDS and Viral Hepatitis (ANRS), the European Commission (Framework Program 7), UK Medical Research Council, US National Institute of Health (NIH), Fondation Plan Alzheimer, Gilead, Tibotec, Boehringer Ingelheim, GlaxoSmithKline, Roche, Pfizer, Merck, Abbott, Bristol-Myers Squibb, Janssen, ViiV Healthcare. However, these grants are managed through her institution and a non-profit society.

Luis Force has received honoraria for advisory boards, a fee for speaking and a fee for organizing education from various pharmaceutical companies including Abbott, Bristol Myers Squibb, Boehringer-Ingelheim, Gilead Sciences, GlaxoSmithKline, Merck and Janssen-Cilag. Timothy Sterling has received research grants from Pfizer, Bristol Myers Squibb and Virco to conduct HIV observational studies. Caroline Sabin has received funding for Advisory Board membership, speaker panels and provision of educational materials for Gilead Sciences, Abbott Pharmaceuticals,

Merck Sharp & Dohme, Janssen-Cilag and Bristol-Myers Squibb. Ole Kirk had prior board membership at Viiv, received payment for lectures and/or for development of educational presentations from Abbott, Gilead and Tibotec/Janssen, and had expenses to travel/accommodations/meetings covered by Abbott, BMS, Gilead, Merck and ViiV. Jonathan Sterne has received payments for educational materials from Gilead Sciences. John Gill has received support for Advisory Board membership from ViiV, Gilead, Abbott, Merck and Janssen.

Table 1. Clinical and demographic characteristics of 5550 eligible HIV individuals, according to CD4 count at end of the virally suppressed period. ART-CC and COHERE HIV multicohort collaboration 2012.

	CD4 count at end of virally suppressed period	
Characteristic	≤200 cells/μL	>200 cells/μL
Number (person-years of observation)	835 (2936)	4715 (17355)
Deaths (mortality rate per 100 PYR)	66 (2.2)	109 (0.6)
Median time from start of cART to start of the suppressed period, months (IQR)	2.8 (1.3-12.1)	2.5 (1.2-5.5)
Age at start of the suppressed period (years)		
<30 (%)	45 (5.4)	512 (10.9)
30-39 (%)	233 (27.9)	1956 (41.5)
40-49 (%)	275 (32.9)	1440 (30.5
>50 (%)	282 (33.8)	907 (17.1)
Route of infection/Gender		
MSM (%)	227 (27.2)	1695 (35.9)
Male heterosexuals (%)	216 (25.9)	995 (21.1)
Female heterosexuals (%)	101 (12.1)	933 (19.8)
IDU (%)	128 (15.3)	489 (10.4)
Other/unknown (%)	163 (18.6)	603 (12.8)
CD4 count at start of the suppressed period		
≤25 (%)	75 (9.0)	223 (4.7)
26-50 (%)	108 (12.9)	370 (7.8)
51 - 100 (%)	268 (32.1)	970 (20.6)
101 -150 (%)	231 (27.7)	1377 (29.2)
151 – 200 (%)	153 (18.3)	1775 (37.6)
Last viral load before start of cART (copies/ml)		
< 100,000 (%)	391 (46.8)	2129 (38.4)
≥ 100,000 (%)	424 (50.8)	2470 (44.5)
VL missing (%)	20 (2.4)	116 (2.5)
Year of start of cART		
1996-1997	69 (8.3)	442 (9.4)
1998 - 2000	336 ()	1686 (35.8)
2001 -	430 (51.5)	2587 (54.9)
Time from cART initiation to start of suppressed period		
<12 months	626 (75.0)	3952 (83.8)
≥12 months	209 (25.0)	763 (16.2)
One or more AIDS events before start of suppressed period (%)		
No AIDS	425 (51.9)	2580 (54.7)
AIDS	410 (49.1)	2135 (45.3)

PYR = person-years at risk; cART = combination antiretroviral therapy; IQR = inter quartile range; MSM = men who have sex with men; IDU = injection drug use; VL = viral load; AIDS = acquired immune deficiency syndrome.

Table 2. Factors associated with failure to achieve CD4 count > 200 cells/μL after three years of viral suppression on cART. ART-CC and COHERE HIV multicohort collaboration 2012.

	Unadjusted odds ratio (95%CI)	Adjusted odds ratio (95%CI)
Age at start of the suppressed period (years)		
<30	1 (reference)	1 (reference)
30-39	1.36 (0.97-1.89)	1.31 (0.93-1.85)
40-49	2.17 (1.56-3.03)	2.04 (1.45-2.88)
≥50	3.98 (2.85-5.55)	4.01 (2.84-5.68)
Route of infection/ Gender		
MSM	1 (reference)	1 (reference)
Male hetero	1.62 (1.32-1.98)	1.50 (1.21-1.85)
Female hetero	0.81 (0.63-1.04)	0.89 (0.68-1.15)
IDU	1.96 (1.54-2.48)	2.03 (1.57-2.61)
Other/unknown	2.02 (1.62-2.52)	1.72 (1.37-2.17)
CD4 count (cells/μL) at start of suppressed period		
≤25	3.90 (2.86-5.32)	5.21 (3.75-7.23)
26-50	3.39 (2.58-4.44)	4.46 (3.35-5.95)
51-100	3.21 (2.59-3.97)	3.73 (2.99-4.68)
101-150	1.95 (1.57-2.42)	2.08 (1.67-2.60)
151-200	1 (reference)	1 (reference)
Last viral load before start of cART **		
< 100,000 copies/ml	1.07 (0.92-1.24)	1.13 (0.97-1.33)
≥100,000 copies/ml	1 (reference)	1 (reference)
Year of start of cART		
1996-1997	1 (reference)	1 (reference)
1998 - 2000	1.28 (0.97-1,69)	1.44 (1.07-1.93)
2001 -	1.07 (0.81-1.40)	1.37 (1.02-1.84)
Time from cART initiation to start of suppressed period		
<12 months	1 (reference)	1 (reference)
≥12 months	1.73 (1.45-2.06)	2.05 (1.68-2.50)
One or more AIDS events before start of suppressed period		
No AIDS	1.17 (1.01-1.35)	0.89 (0.76-1.04)
AIDS	1 (reference)	1 (reference)

MSM = men who have sex with men; IDU = injection drug use; cART = combination antiretroviral therapy; AIDS = acquired immune deficiency syndrome.

* Adjusted for all other covariates listed in the table.

** 136 individuals had no baseline VL and were included in the analysis as missing VL.

Table 3. Mortality hazard ratios comparing individuals with CD4 count ≤200 and >200 cells/μL at the end of suppressed period, overall and stratified on CD4 count at start of suppressed period, age, mode of transmission and AIDS defining events. ART-CC and COHERE HIV multicohort collaboration 2012.

Strata	Deaths (N)		Person-time of observation (years)		Crude HR (95%CI)	Adjusted* HR (95%CI)
	≤200 cells/μL	>200 cells/μL	≤200 cells/μL	>200 cells/μL		
All individuals	66	109	2937	17346	3.35 (2.46-4.57)	2.60 (1.86-3.61)
Strata: Age (years)						
<30	1	2	154	1826	NA	NA
30-39	8	25	863	7457	3.00 (1.33-6.76)	3.01 (1.26-7.16)
40-49	19	40	937	5174	2.50 (1.44-4.34)	2.04 (1.12-3.70)
≥50	38	42	983	2889	2.51 (1.61-3.93)	3.18 (1.96-5.14)
Strata: Route of transmission/ Gender						
MSM	13	30	84	6694	3.58 (1.85-6.93)	2.62 (1.28-5.34)
Male heterosexual	14	25	729	3516	2.86 (1.47-5.57)	2.41 (1.19-4.86)
Female heterosexual	7	7	298	2975	8.21 (2.80-24.05)	NA
IDU	12	27	461	1810	1.60 (0.78-3.27)	1.43 (0.65-3.17)
Other/unknown	20	20	605	2350	3.13 (1.68-5.83)	2.53 (1.26-5.07)
Strata: CD4 count at start of suppressed period						
≤25 cells/μL	6	2	317	904	NA	NA
26-50 cells/μL	6	5	452	1386	2.92 (0.86-9.93)	2.76 (0.66-11.46)
51-100 cells/μL	17	26	973	3731	2.56 (1.35-4.85)	1.43 (0.71-2.88)
101-150 cells/μL	22	40	735	5022	3.40 (2.00-5.75)	2.62 (1.49-4.60)
151-200 cells/μL	15	36	459	6303	5.57 (3.01-10.32)	3.82 (1.95-7.45)
Strata: Last viral load before start of cART						
Viral load <100,000 copies/ml	30	51	1365	7520	2.98 (1.88-4.72)	2.23 (1.34-3.72)
Viral load ≥100,000 copies/ml	33	58	1517	9504	3.19 (2.06-4.94)	2.61 (1.63-4.18)

Strata: Year of cART initiation						
1996-1997	8	22	394	2750	2.87 (1.24-6.64)	2.25 (0.87-5.84)
1998-2000	40	56	1535	8453	3.65 (2.42-5.51)	2.74 (1.74-4.30)
2001-	18	31	1008	6143	3.39 (1.87-6.14)	3.03 (1.62-5.65)
Strata: Time from cART initiation to start of suppressed period						
<12 months	18	18	573	2336	3.04 (2.13-4.33)	2.51 (1.23-5.14)
≥12 months	48	91	2363	15010	3.96 (2.03-7.70)	2.53 (1.72-3.70)
Strata: One or more AIDS events by end of suppressed period						
No AIDS	28	48	13507	8584	3.51 (2.18-5.64)	2.49 (1.47-4.20)
AIDS	38	61	1587	8762	3.05 (2.02-4.61)	2.47 (1.59-3.83)

HR = hazard ratio; MSM = men who have sex with men; IDU = injection drug use; cART = combination antiretroviral therapy; AIDS = acquired immune deficiency syndrome.

* Adjusted for all other covariates listed in the table. Stratification factor removed from list of adjustments.

NA: numbers in these strata were too small for an analysis to be performed

Table 4. Cause-specific hazard ratios comparing HIV individuals (ART-CC only) with CD4 count ≤200 vs. >200 cells/μL at end of suppressed period. ART-CC and COHERE HIV multicohort collaboration 2012.

Causes of death	Number (%) of deaths according to CD4 count at end of suppressed period		HR (95% confidence interval)	
	≤200 cells/μL	>200 cells/μL	Unadjusted	Adjusted*
All	41 (100)	80 (100)	3.05 (2.10- 4.44)	2.52 (1.71-3.70)
AIDS defining causes of death	4 (9.8)	7 (8.8)	3.39 (0.99-11.57)	2.75 (0.78-9.69)
Non-AIDS defining causes of death	26 (63.4)	49 (61.3)	3.14 (1.95-5.06)	2.61 (1.61-4.23)
Hepatitis	5	5	5.95 (1.72-20.56)	6.76 (1.93-23.74)
Non-AIDS cancer	14	23	3.50 (1.73-6.95)	2.89 (1.44-5.28)
Other causes of death**	6	21	1.69 (0.68-4.18)	1.24 (0.50-3.12)
Unnatural causes of death	3 (7.3)	8 (10.0)	2.27 (0.60-8.57)	2.07 (0.54-7.97)
Unknown causes of death	8 (19.5)	16 (19.5)	3.00 (1.28-7.01)	2.34 (0.98-5.59)

HR = hazard ratio; AIDS = acquired immune deficiency syndrome.

*Adjusted for gender and age (<=50 years vs. >50 years)

**Other causes of death for patients with CD4 count ≤200 cells/μL were; 2 related to infection, 2 related to cardiovascular disease, 2 related to digestive system disease. Other causes of death for patients with CD4 count >200 cells/μL were related to infection (5) lung diseases (2), cardiovascular diseases (9), digestive system diseases (2), central nervous system diseases (2) and renal diseases (1).

Figure 1. Flowchart and study timeline. ART-CC and COHERE HIV multicohort collaboration 2012.

Figure 2. Cumulative probability of survival stratified by CD4 count at the end of the virally suppressed period: 1) CD4 ≤200 cells/µL (full line), 2) 200 <CD4 ≤ 350 cells/µL (broken line), 3) 350 < CD4 ≤500 cells/µL (dotted line) and 4) CD4>500 cells/µL (broken and dotted line). ART-CC and COHERE HIV multicohort collaboration 2012.

**Dear editorial staff. I have attached the TIFF but I was not able to explain the 4 categories under Number at risk in the statistic program why I previously have used a word box, as seen below. How do we fix this?

CD4 ≤200 ——
200 < CD4 ≤350 -----
350 < CD4 ≤500 ·····
CD4>500 —·—·

References

Reference List

(1) Lohse N, Hansen AB, Pedersen G, Kronborg G, Gerstoft J, Sorensen HT et al. Survival of persons with and without HIV infection in Denmark, 1995-2005. Ann Intern Med 2007; 146(2):87-95.

(2) El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med 2006; 355(22):2283-2296.

(3) The CASCADE Collaboration. Survival after introduction of HAART in people with known duration of HIV-1 infection. Concerted Action on SeroConversion to AIDS and Death in Europe. Lancet 2000; 355(9210):1158-1159.

(4) Moore RD, Keruly JC. CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. Clin Infect Dis 2007; 44(3):441-446.

(5) Baker JV, Peng G, Rapkin J, Krason D, Reilly C, Cavert WP et al. Poor initial CD4+ recovery with antiretroviral therapy prolongs immune depletion and increases risk for AIDS and non-AIDS diseases. J Acquir Immune Defic Syndr 2008; 48(5):541-546.

(6) Hughes RA, Sterne JA, Walsh J, Bansi L, Gilson R, Orkin C et al. Long-term trends in CD4 cell counts and impact of viral failure in individuals starting antiretroviral therapy: UK Collaborative HIV Cohort (CHIC) study. HIV Med 2011; 12(10):583-593.

(7) Grabar S, Le M, V, Goujard C, Leport C, Kazatchkine MD, Costagliola D et al. Clinical outcome of patients with HIV-1 infection according to immunologic and virologic response after 6 months of highly active antiretroviral therapy. Ann Intern Med 2000; 133(6):401-410.

(8) Engsig FN, Gerstoft J, Kronborg G, Larsen CS, Pedersen G, Roge B et al. Long-term mortality in HIV patients virally suppressed for more than three years with incomplete CD4 recovery: a cohort study. BMC Infect Dis 2010; 10:318.

(9) Young J, Psichogiou M, Meyer L, Ayayi S, Grabar S, Raffi F et al.CD4 cell count and the risk of AIDS or death in HIV-Infected adults on combination antiretroviral therapy with a suppressed viral load: a longitudinal cohort study from COHERE. PLoS Med 2012; 9(3):e1001194.

(10) Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet 2002; 360(9327):119-129.

(11) Frank de Wolf, Caroline Sabin, le Ki, Claire Thor, Genevieve Chene, Kholoud Port. Developing a multidisciplinary network for clinical research on HIV infection: the EuroCoord experience. Clinical Investigation 2012; 2(3):255-264.

(12) Gill J, May M, Lewden C, Saag M, Mugavero M, Reiss P et al. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996-2006: collaborative analysis of 13 HIV cohort studies. Clin Infect Dis 2010; 50(10):1387-1396.

(13) Jason P.Fine, Robert J.Gray. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association 1999; 94(446):496-509.

(14) Rubin D. Inference and missing data. Biometrika 1976; 63(3):581-592.

(15) NIH. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and adolescents. 2013. 28-10-2013. Ref Type: Online Source. http://aidsinfo.nih.gov/guidelines

(16) Chene G, Sterne JA, May M, Costagliola D, Ledergerber B, Phillips AN et al. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. Lancet 2003; 362(9385): 679–86.

(17) Lanoy E, May M, Mocroft A, Phillip A, Justice A, Chene G et al. Prognosis of patients treated with cART from 36 months after initiation, according to current and previous CD4 cell count and plasma HIV-1 RNA measurements. AIDS 2009; 23(16):2199-2208.

(18) Kaufmann GR, Bloch M, Finlayson R, Zaunders J, Smith D, Cooper DA. The extent of HIV-1-related immunodeficiency and age predict the long-term CD4 T lymphocyte response to potent antiretroviral therapy. AIDS 2002; 16(3):359-367.

(19) Hunt PW, Deeks SG, Rodriguez B, Valdez H, Shade SB, Abrams DI et al. Continued CD4 cell count increases in HIV-infected adults experiencing 4 years of viral suppression on antiretroviral therapy. AIDS 2003; 17(13):1907-1915.

(20) Florence E, Lundgren J, Dreezen C, Fisher M, Kirk O, Blaxhult A et al. Factors associated with a reduced CD4 lymphocyte count response to HAART despite full viral suppression in the EuroSIDA study. HIV Med 2003; 4(3):255-262.

(21) Dion ML, Bordi R, Zeidan J, Asaad R, Boulassel MR, Routy JP et al. Slow disease progression and robust therapy-mediated CD4+ T-cell recovery are associated with efficient thymopoiesis during HIV-1 infection. Blood 2007; 109(7):2912-2920.

(22) Yamashita TE, Phair JP, Munoz A, Margolick JB, Detels R, O'Brien SJ et al. Immunologic and virologic response to highly active antiretroviral therapy in the Multicenter AIDS Cohort Study. AIDS 2001; 15(6):735-746.

(23) Khoury G, Rajasuriar R, Cameron PU, Lewin SR. The role of naive T-cells in HIV-1 pathogenesis: an emerging key player. Clin Immunol 2011; 141(3):253-267.

(24) Loutfy MR, Genebat M, Moore D, Raboud J, Chan K, Antoniou T et al. A CD4+ cell count <200 cells per cubic millimeter at 2 years after initiation of combination antiretroviral therapy is associated with increased mortality in HIV-infected individuals with viral suppression. J Acquir Immune Defic Syndr 2010; 55(4):451-459.

(25) Guiguet M, Boue F, Cadranel J, Lang JM, Rosenthal E, Costagliola D. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. Lancet Oncol 2009; 10(12):1152-1159.

(26) Monforte A, Abrams D, Pradier C, Weber R, Reiss P, Bonnet F et al. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. AIDS 2008; 22(16):2143-2153.

(27) Reekie J, Kosa C, Engsig F, Monforte A, Wiercinska-Drapalo A, Domingo P et al. Relationship between current level of immunodeficiency and non-acquired immunodeficiency syndrome-defining malignancies. Cancer 2010; 116(22):5306-5315.

(28) Gascon RL, Narvaez AB, Zhang R, Kahn JO, Hecht FM, Herndier BG et al. Increased HLA-DR expression on peripheral blood monocytes in subsets of subjects with primary HIV infection is associated with elevated CD4 T-cell apoptosis and CD4 T-cell depletion. J Acquir Immune Defic Syndr 2002; 30(2):146-153.

(29) Kuller LH, Tracy R, Belloso W, De WS, Drummond F, Lane HC et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med 2008; 5(10):e203.

(30) Riddler SA, Haubrich R, DiRienzo AG, Peeples L, Powderly WG, Klingman KL et al. Class-sparing regimens for initial treatment of HIV-1 infection. N Engl J Med 2008; 358(20):2095-2106.

(31) Abrams D, Levy Y, Losso MH, Babiker A, Collins G, Cooper DA et al. Interleukin-2 therapy in patients with HIV infection. N Engl J Med 2009; 361(16):1548-1559.

(32) Khanna N, Opravil M, Furrer H, Cavassini M, Vernazza P, Bernasconi E et al. CD4+ T cell count recovery in HIV type 1-infected patients is independent of class of antiretroviral therapy. Clin Infect Dis 2008; 47(8):1093-1101.